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Do fatigue and UDCA therapy truly have independent effects on mortality in PBC?

To the Editor:

We read with interest the paper by Jones *et al.* [1] regarding the impact of fatigue and ursodeoxycholic acid (UDCA) treatment on mortality in PBC. The authors are to be congratulated on their accrual and close follow up of a well characterised group of patients and their efforts have certainly expanded further our understanding of the natural history and the effects of pharmacological interventions in PBC.

Nonetheless, caution must be exercised when evaluating their dataset and conclusions, particularly in respect of the independent effect of fatigue and UDCA usage on mortality for the following reasons.

Firstly, whilst on univariate analysis both the presence of fatigue (which, importantly was identified here as a categorical variable) and lack of use of UDCA were associated with increased mortality, only 43 deaths were recorded. Consequently, the analysis of seven different variables in the Cox regression model is possibly excessive and could lead to statistical errors in its output as the "rule of thumb" of regression analysis has historically been a minimum of 10 outcome events per variable. However, recent reports suggesting the use of 5–9 outcomes per variable only uncommonly lead to statistical error, though is slightly more common with Cox models [2].

Secondly, fatigue, previously identified as categorical (present or absent), is now interpreted as a linear score (based on the FIS) as part of the Cox model. Therefore, although a 1 point increase in the FIS is independently associated with an increased mortality (risk ratio 1.008), how the presence (or otherwise) of fatigue affects mortality in an independent model is not certain.

Thirdly, and perhaps most crucially, in this model, UDCA therapy was not independently predictive of improved mortality at all with a risk ratio of 0.728 (95% CI 0.370–1.432) $p = 0.357$. This issue is of fundamental importance as it is at variance with the very title of the manuscript.

On a final note, the results in Table 1 suggests a possible typographical error in regard to the effect of age on mortality. The initial B value would suggest an increased risk for age and, therefore, a risk ratio of >1, especially given the highly significant p value. However, the risk ratio of 0.728% and 95% CI of 0.37–1.432 cannot provide such a highly significant p value, given the 95% CI clearly crosses 1.

In summary, whilst it remains possible that fatigue is *independently* associated with increased mortality in PBC, the data presented by Jones *et al.* in its published format does not prove that this is the case in respect of the presence or otherwise of fatigue. Furthermore, the use of UDCA therapy cannot be said to have any independent effect on mortality, based on the published data.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] Jones DE, Al-Rifai A, Frith J, Patanwala I, Newton JL. The independent effects of fatigue and UDCA therapy on mortality in primary biliary cirrhosis: results of a 9 year follow-up. J Hepatol 2010;53:911–917.
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Reply to: Do fatigue and UDCA therapy truly have independent effects on mortality in PBC?

To the Editor:

We thank Drs. Yousuf and Yeoman for their appreciation of our work and interest in our recent paper [1] regarding the impact of fatigue and ursodeoxycholic acid (UDCA) treatment on mortality in PBC. Although they raise some interesting points, we believe they may not fully understand the conclusions we made in our paper. This is the largest series of patients with PBC followed up for a considerable period of time, and this cohort has provided important insights into the true impact that fatigue has on not only quality of life but also length of life.

Yousuf and Yeoman are correct, COX models can theoretically be limited in their interpretation as the number of variables is increased. If we had used this as our only analysis, we may have agreed with them; however, combined with the Kaplan Meier and Log Rank Test Analysis, which confirm the relationship between fatigue and mortality, we believe this enhances the

power of the COX models considerably and should be interpreted as underlining our findings.

In order to perform the Kaplan Meier analysis it was necessary to dicotomise the groups into those with and without fatigue. The rationale for this was described fully in the original description of the cohort [2]. The COX model allowed us to explore the absolute level of FIS score. Both analyses confirmed the relationship between fatigue and mortality and, therefore, we cannot understand how Yousaf and Yeoman can now suggest "how the presence (or otherwise) of fatigue affects mortality in an independent model is not certain".

The authors are correct, in the COX model UDCA therapy was not independently predictive of improved mortality and on the basis of this they refute our conclusions regarding UDCA. We believe inclusion of categorical data into a COX model is a blunt instrument and we would direct Yousuf and Yeoman to the other analyses in the results section which clearly show that the effect that UDCA response has upon mortality is clearly independent of the effect that fatigue status has. This is an important message for clinicians managing patients with PBC in that it confirms that non-fatigued patients who are UDCA responders are at very low risk. This is one of the key messages from the paper.

In summary, we question what further data the authors consider required to confirm to them that it has now gone from beyond the "possible that fatigue is *independently* associated with increased mortality in PBC" if they believe that our well characterised comprehensively collected geographically defined cohort does not "prove that this is the case in respect of the presence or otherwise of fatigue". Furthermore we would suggest that we clearly show, albeit in a small cohort, that response to UDCA therapy has an effect on mortality.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] Jones DE, Al-Rifai A, Frith J, Patanwala I, Newton JL. The independent effects of fatigue and UDCA therapy on mortality in primary biliary cirrhosis: results of a 9 year follow-up. J Hepatol 2010;53:911–917.
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SLC40A1-R178G mutation and ferroportin disease

To the Editor:

In their excellent systematic meta-analysis on the ferroportin disease, recently published in the *Journal of Hepatology*, Mayr *et al.* present in detail all the described *SLC40A1* gene alterations and their relationship with disease phenotype [1]. The prevalence of these alterations in the general population is also presented, indicating that a few of them are polymorphisms with an unknown, as yet, biological significance.

Amongst these alterations, the authors include the mutation *SLC40A1*-R178G, described by us in a Greek family with ferroportin disease [2], despite the fact that they refer regarding this mutation (Table 3), obviously by mistake, to another publication. To this end, it is interesting to present information derived from the 2-year follow-up of the affected members of this family, as well as the data missing from the literature population that we have acquired in the mean time, indicating that the *SLC40A1*-R178G mutation is not a polymorphism. Instead, they support our position that it represents a novel mutation resulting in classical ferroportin disease with a mild, and rather variable, phenotype.

In our previous publication, the *SLC40A1*-R178G mutation was found to be responsible for a classical ferroportin disease phenotype in a 25-year-old female [2], who remains in excellent condition being subjected to periodical venesections every three months. Examining the family tree, we detected the same mutation in the proband's 53-year-old mother, presenting with slight hyperferritinemia and liver hemosiderosis of moderate degree. During the follow-up, her hyperfirretinemia worsened, necessitating therapeutic venesections. The *SLC40A1*-R178G mutation was also detected in the proband's 87-year-old grandfather who displayed low transferrin saturation, but not hyperferritinemia. Because of his old age, this patient, the oldest one in the literature diagnosed with ferroportin disease, was not submitted to further evaluation regarding the possible coexistence of iron deficiency. Two years after the diagnosis, he remains alive without needing venesections.

Following this atypical presentation of ferroportin disease and considering that the *SLC40A1*-R178G mutation had not been observed in large comprehensive population studies [3–5], we questioned whether it was a functional polymorphism prevalent in the Greek population.

To this end, we analyzed 253 bone marrow donors (male/female: 123/130, mean age: 34.7 years, range: 21–60) from Central Greece area. All subjects provided written informed consent, while the study was conducted in accordance with the principles of Helsinki declaration and was approved by the Institutional Review Board of the University Hospital of Larissa, Greece. Genomic DNA was extracted from peripheral blood using the QIAamp